Pharmacological Study of Compounds of the Invention

EXAMPLE 43

In vitro Activity

[0397] L1210 Murine Leukaemia

[0398] L1210 murine leukaemia was used in vitro. The cells are cultured in RPMI 1640 complete culture medium containing 10% foetal calf serum, 2 mM glutamine, 50 units/ml of penicillin, 50 μg/ml of streptomycin and 10 mM Hepes, pH=7.4. The cells are distributed on microplates and are exposed to the cytotoxic compounds for 4 doubling periods, or 48 hours. The number of viable cells is then quantified by a colorimetric assay, the Microculture Tetrazolium Assay (J. Carmichael et al., *Cancer Res.;* 47, 939-942 (1987)). The results are expressed as the IC_{50}, the concentration of cytotoxic agent which inhibits the treated cells by 50%. All the compounds of the invention exhibit good cytotoxicity with respect to this cell line. By way of example, the compound of Example 20 has an IC_{50} of 0.074 μM with respect to L1210.

[0399] Human Cell Lines

[0400] The compounds of the invention were also tested on human cell lines originating from solid tumours, in accordance with the same test protocol as that described for L1210 murine leukaemia but with incubation periods of 4 days instead of 2 days. By way of illustration, the compound of Example 20 has an IC_{50} of 190 nM with respect to DU145 prostate carcinoma and of the order of from 10 to 200 nM with respect to human lines originating from A549 non-small-cell lung carcinoma, HT-29 colon carcinoma and KB-3-1 epidermoid carcinoma.

EXAMPLE 44

Action on the Cell Cycle

[0401] L1210 cells are incubated for 21 hours at 37° C. in the presence of various concentrations of test compounds. The cells are then fixed by 70% (v/v) ethanol, washed twice in PBS and incubated for 30 minutes at 20° C. in PBS that contains 100 μg/ml of RNAse and 50 μg/ml of propidium iodide. The results are expressed in terms of the percentage of the cells that accumulate in the G2+M phase after 21 hours, compared with the control (control: 20%). The compounds of the invention are especially interesting, at a concentration of less than 2.5 μM causing accumulation of at least 70% of cells in the G2+M phase after 21 hours.

EXAMPLE 45

In vivo Activity

Anti-Tumour Activity on P 388 Leukaemia

[0402] Line P388 (murine leukaemia) was supplied by the National Cancer Institute (Frederick, USA). The tumour cells (10^6 cells) were inoculated on day 0 into the peritoneal cavity of female B6D2F1 mice (Iffa Credo, France). Six mice weighing from 18 to 20 g were used in each test group. The products were administered by the intraperitoneal route on day 1.

[0403] The anti-tumour activity is expressed as % T/C:

$$\%\ T/C\ (\text{mouse}) = \frac{\text{Median survival time of the treated animals}}{\text{Median survival time of the control animals}} \times 100$$

[0404] The results obtained show excellent in vivo activity in the P 388 leukaemia model, with a T/C of 210% for a dose of 50 mg/kg, along with low toxicity of the compounds, indicating an excellent therapeutic index.

EXAMPLE 46

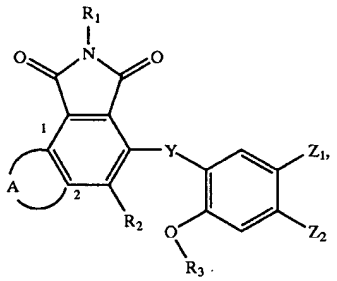
Pharmaceutical Composition: Injectable Solution

[0405] Compound of Example 20 . . . 10 mg

[0406] Distilled water for injectable preparations . . . 0.25 ml

1. Compounds of formula (I):

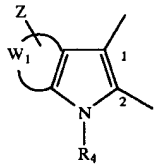
(I)



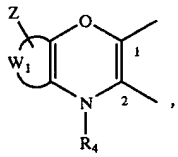
wherein:

A, together with the carbon atoms to which it is bonded, represents a group of formula (a) or (b):

(a)



(b)



wherein:

W_1, together with the carbon atoms to which it is bonded, represents a phenyl group or a pyridyl group,

Z represents a group selected from hydrogen and halogen atoms and the groups linear or branched (C_1-C_6)alkyl, nitro, cyano, hydroxy, linear or branched (C_1-C_6)alkoxy, aryl, aryl-(C_1-C_6)alkyl (in which the alkyl moiety is linear or branched), aryloxy and aryl-(C_1-C_6)alkoxy (in which the alkoxy moiety is linear or branched) and NR_5R_6 wherein R_5 and R_6, which are identical or different, each inde-